Remarks

Claims 45-56 are pending in the subject application. By this Amendment, Applicants have added new claims 59-64, amended claims 45 and 52 and canceled claim 49, 51 and 53. Support for the amendments and new claims can be found throughout the subject specification and in the claims as originally filed (see, for example, the original claims of the PCT application, previously pending claim 49 and the as-filed specification at pages 5-9 ). Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 45-48, 50, 52, 54-56 and 59-64 are currently before the Examiner with claims 62-64 standing withdrawn from consideration. Favorable consideration of the pending claims is respectfully requested.

At the time this matter is taken up for consideration, Applicants respectfully request the courtesy of an interview to discuss the rejection of record in view of the claim amendments and arguments presented in this response.

Claims 45-49, 51 and 53-56 remain rejected under 35 U.S.C. § 103(a) as obvious over Ashkenazi *et al.* (WO 99/53059) in view of Patel *et al.* (WO 00/52158). In response to Applicants' arguments, the Office Action indicates that there is no indication in the specification that the particulars of the instant promoter is an advancement over the art that was achieved with unexpected consequences or otherwise unexpected results. Based upon the teachings of the cited references, "the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention." The Office Action notes that Ashkenazi *et al.* teach a molecule comprising a signal sequence operably linked to a tPA pro-peptide to form a "signalpro" sequence. The signal sequence can be any signal sequence so long as it performs the function of directing the protein to the lumen of the ER. The tPA sequence is designed for secretion of the peptide. Hence, similar to the instant invention, Ashkenazi *et al.* are drawn to a signal-pro sequence to improve secretion and production of the linked protein sequences. The Office Action states that Ashkenazi et *al.* do not teach use of murine IgSP but Patel *et al.* is directed towards use of murine IgSP sequences in recombinant fusion sequences wherein the construct further comprises a secretion sequence. Therefore, Ashkenazi *et al.* and Patel *et al.* are directed to overlapping inventions wherein the format is a leader (signal) sequence-export signal. The specifics of each differ but taken together one would conclude that the signal sequence of Patel *et al.* would function as a heterologous sequence as

encompassed by Ashkenazi *et al.* Finally, it is noted that the Office Action argues that it is within the ordinary skill of the art to use available methodologies to isolate a variety of sequences comprising any of a number of promoters and one would have been motivated to do so in order to modify sequences by applying conventional methodologies. Particularly, the Office Action argues that the Supreme Court (in *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 U.S.P.Q.2d 1385 (2007)) emphasized a "need for caution in granting a patent based on a combination of elements found in the prior art". Applicants note, however, that the Office Action appears to ignore a number of other principals also set forth in that decisions. For example, "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" (*KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741, 82 U.S.P.Q.2d 1385, 1396 (2007).

Applicants respectfully assert that the claimed invention is not obvious over the cited references. As noted previously, it is unclear what motivation one of ordinary skill in the art would have had to combine an immunoglobulin signal peptide with a tPA propeptide consisting of amino acids 23-32 of SEQ ID NO: 2 without the guidance and disclosure of the presently claimed invention. Indeed, the Office Action argues that one skilled in the art would have been motivated to use a variety of signal sequences because that individual would have had the ability to modify the sequences using conventional methodologies (Final Rejection at page 4).

The Office Action further argues that Ashkenazi *et al.* teach the use of a signal-pro sequence to improve secretion and production of the linked protein sequences (Final Rejection at page 6) and that Ashkenazi *et al.* further suggest the addition of other (unidentified) signal peptides to the tPA propeptide sequences disclosed in the reference. Based on this articulated reasoning in the Office Action, it is unclear what motivation exists to modify the teachings of Ashkenazi *et al.* with those of Patel *et al.* since there is no indication that the Ashkenazi *et al.* sequences require improved secretion characteristics. At best, one skilled in the art would have been motivated to substitute the signal and propeptide disclosed in Ashkenazi *et al.* with the murine IgSP sequence disclosed in Patel *et al.* since

those elements could be considered equivalent to one another for directing protein secretion. However, no rationale has been provided or articulated in the Office Action explaining why one would add the IgSP disclosed in Patel *et al.* to the full construct disclosed in Ashkenazi *et al.* Applicants further submit that following the teachings of Ashkenazi *et al.*, one of ordinary skill in the art seeking to produce a heterologous polypeptide "X" would have been motivated to use either the tPA propeptide or combine the signal peptide of the polypeptide "X" with the tPA propeptide in order to form a construct for the secretion of the polypeptide "X". Applicants respectfully assert that any suggestion to create the claimed construct could only be arrived at through hindsight reconstruction which is improper.

Even assuming, *arguendo*, that a *prima facie* case of obviousness has been established, Applicants further submit that the claimed invention provides for unexpectedly improved secretion of fusion proteins. As indicated in Example 1.2 and Figure 4, the "IgSp-tPA signal propeptide is able to boost secretion of TBPI from cells as demonstrated by the increased amount of TBPI detected in the supernatant versus the amount of TBPI detected in intracellular compartments. Thus the IgSP-tPA-TBPI construct, comprising TBPI fused to an IgSP-tPA propeptide, increases secretion of TBPI compared to the constructs corresponding to the TBPI protein fused to the IgSP signal peptide, to the secreted alkaline phosphatase signal peptide or to the growth hormone signal peptide." Additionally, Example 2.2 demonstrates that "pools of IgSP-tPA-TBPI expressing cells had higher titers of TBPI than pools of tPA-TBPI expressing cells. The results clearly indicate that the IgSP-tPA construct is at least two fold better than tPA construct in terms of quantity of secreted protein that is produced." It is further noted that this effect was also observed with another protein (the interferon gamma receptor chain protein) as set forth in Example 3.2. In a CMV vector, the IgSP-tPA pre-propeptide was about 2.3 fold more efficient in promoting secretion of the IFNAR protein in the supernatant than the native IFNAR signal peptide. The IgSP-tPA pre-propeptide was about 4.3 fold more efficient in promoting secretion of the IFNAR protein in the supernatant than the native IFNAR signal peptide when tested in constructs comprising the promoter of the mCMV-IE2 gene. Such improved secretion of heterologous protein could not have been predicted or expected on the basis of the cited combination of references.

Applicants note the Examiner's comments in the Advisory Action regarding the comparison of a fusion protein comprising IgSP-tPA-TNFR (TBPI) versus a fusion protein of tPA-TNFR (TBPI). Such a comparison was discussed in the last response and is found in Example 2.2. As noted therein, such the claimed invention (IgSP-tPA construct) resulted increased secretion of TNFR as compared to the tPA construct (the increase was at least two fold, see page 14, Example 2.2 and Figure 6). It is, again, respectfully submitted that these results would not have been expected in view of the cited references. Accordingly, reconsideration and withdrawal of the obviousness rejection of record is respectfully requested.

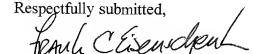
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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